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Unlocking Parkinson's Disease

what's new in research and diagnosis

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Disclosures

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Goals for today

- To define PD and its pathology
- To describe our current options
- To outline what's new in diagnosis and treatment

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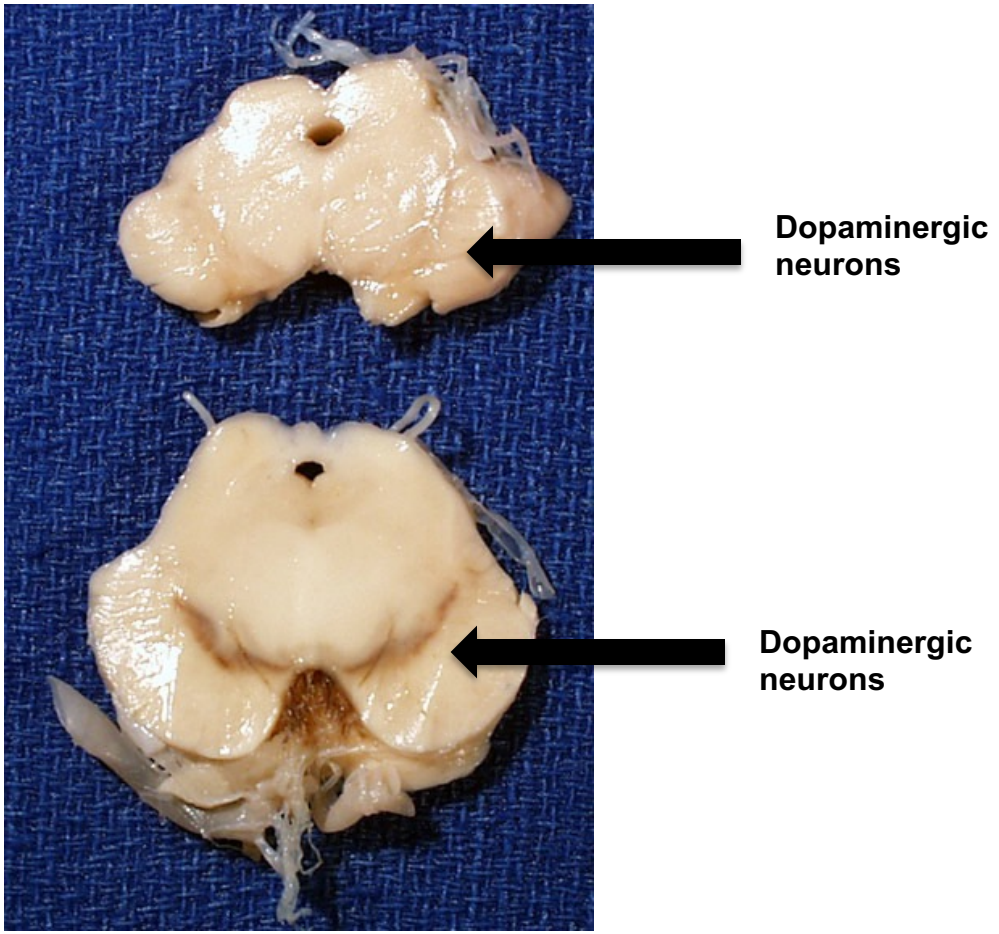
Parkinson's disease

What is it?

Parkinson's disease – what is it?

- Parkinson's disease is a clinical diagnosis
- It is disease primarily of loss of dopamine
- 60-80% of the dopamine producing neurons are lost before the motor signs of PD emerge
- Non-motor signs often emerge before motor signs
- Dopaminergic neurons are dopamine banks
  - They release what you need
  - and store excess



Recognizing Parkinson's disease

- Cardinal features of PD:
  - Motor:
    - Rest tremor
    - Bradykinesia
    - Rigidity
    - Postural instability

Recognizing Parkinson's disease

- Cardinal features of PD:
  - Motor:
    - Rest tremor
      - Onset is usually in the hand
      - asymmetric
      - Improves with movement
    - Bradykinesia
    - Rigidity
    - Postural instability

Recognizing Parkinson's disease

- Cardinal features of PD:
  - Motor:
    - Rest tremor
    - Bradykinesia
      - Slowed movement
      - Decreased facial expression
      - Decreased manual dexterity
      - Decreased stride length and armswing
    - Rigidity
    - Postural instability

Recognizing Parkinson's disease

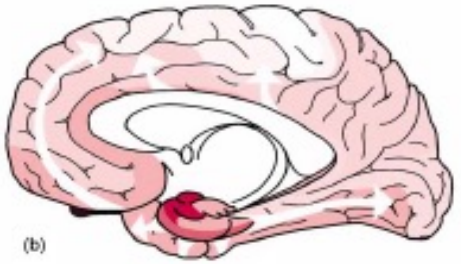
- Cardinal features of PD:
  - Motor:
    - Rest tremor
    - Bradykinesia
    - Rigidity
      - Muscles resist movement
      - frequently described by patients as weakness or soreness.
    - Postural instability

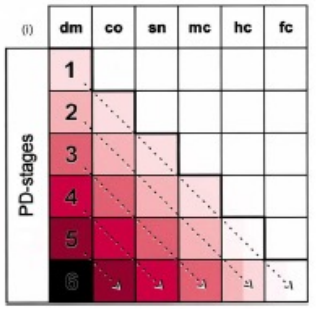
Recognizing Parkinson's disease

- Cardinal features of PD:
  - Motor:
    - Rest tremor
    - Bradykinesia
    - Postural instability
      - Stoop/forward lean
      - Festination/retropulsion

Parkinson's disease

- What underlies the disease?
- Accumulation of an abnormally folded protein: alpha synuclein
- Accumulation starts in two places simultaneously
  - Olfactory bulb
  - Medulla
- Gradually involves adjacent areas





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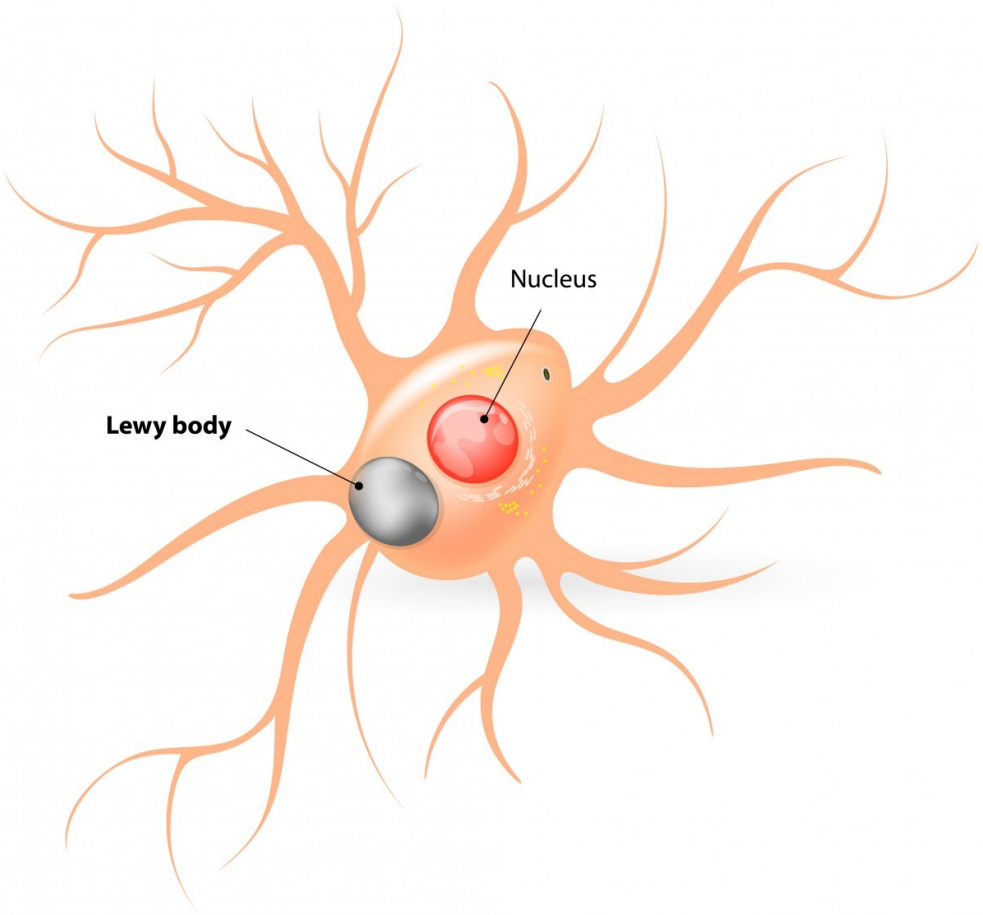
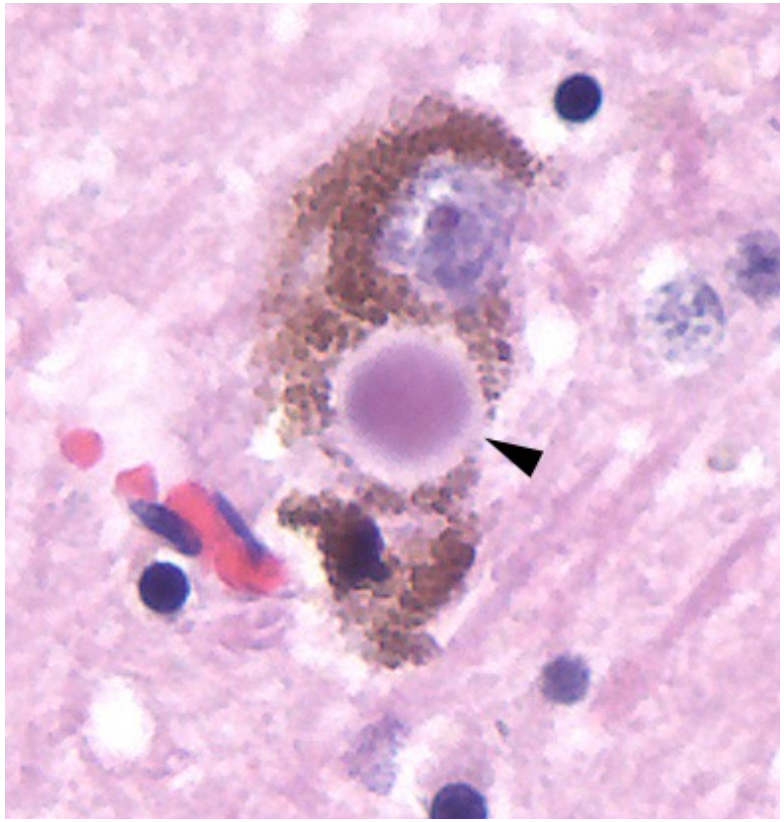
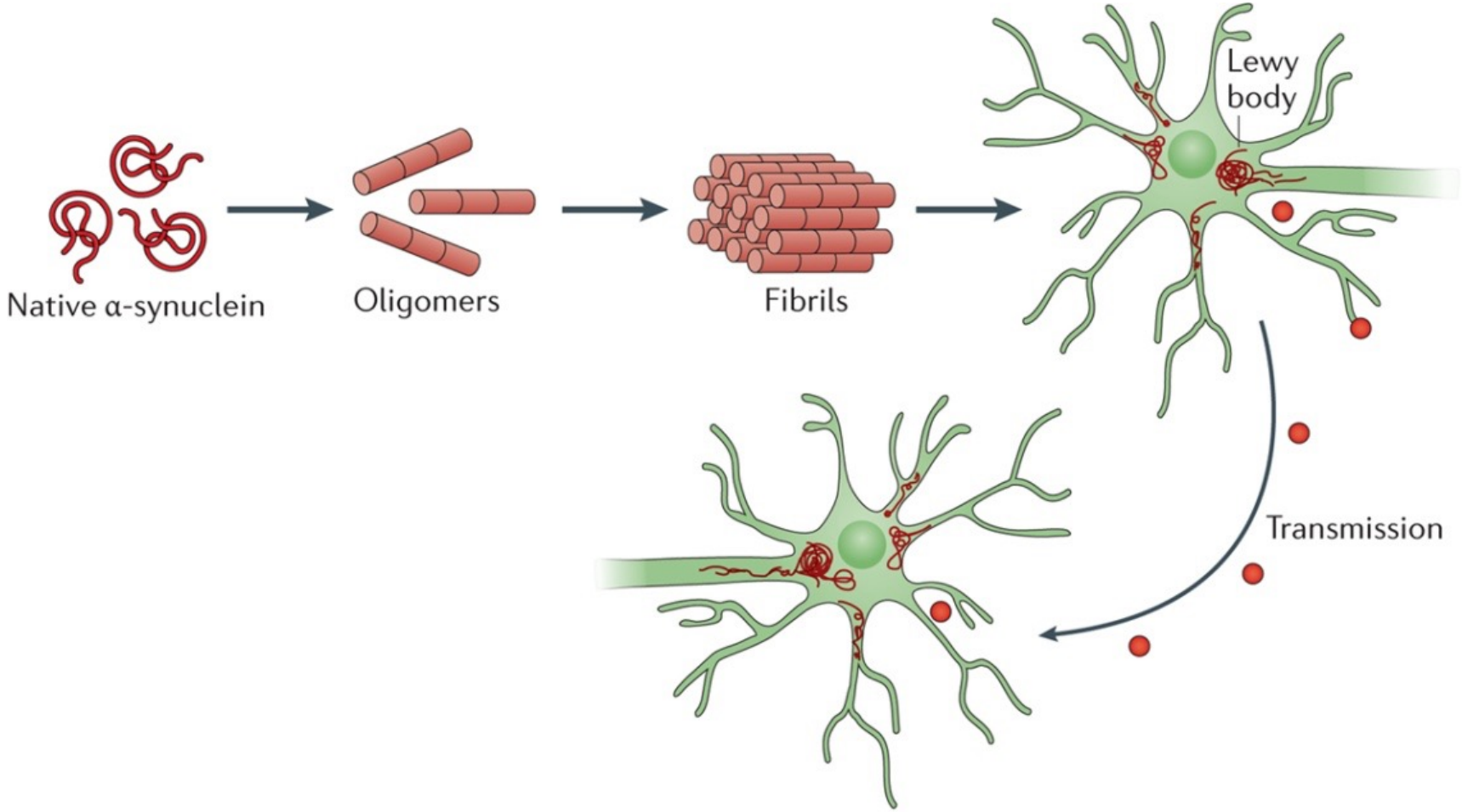
Heiko Braak et al. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiology of Aging. 2003; 24:197-211


Nucleus
Lewy body



Parkinson's disease: causes



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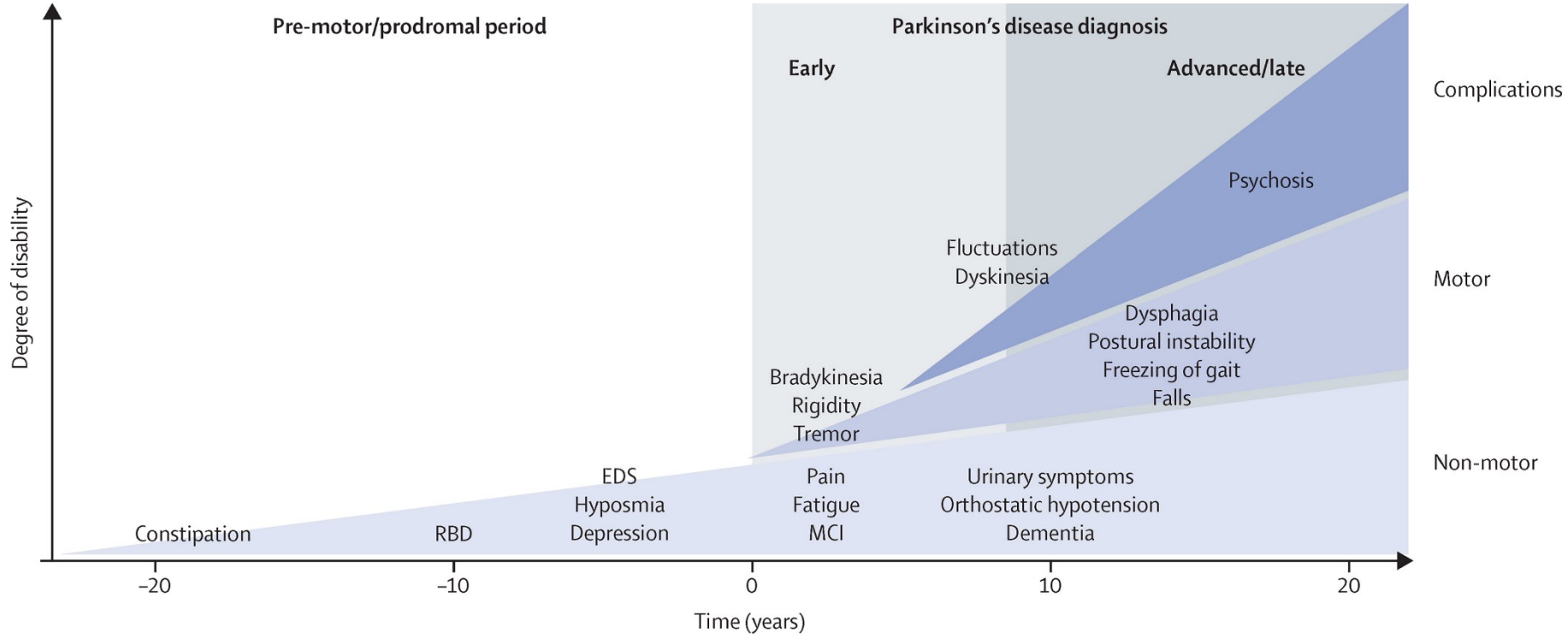
Kingwell, K. Zeroing in on neurodegenerative α-synuclein. Nat Rev Drug Discov 16, 371–373 (2017)



L Kalia, A Lang. The Lancet 2015

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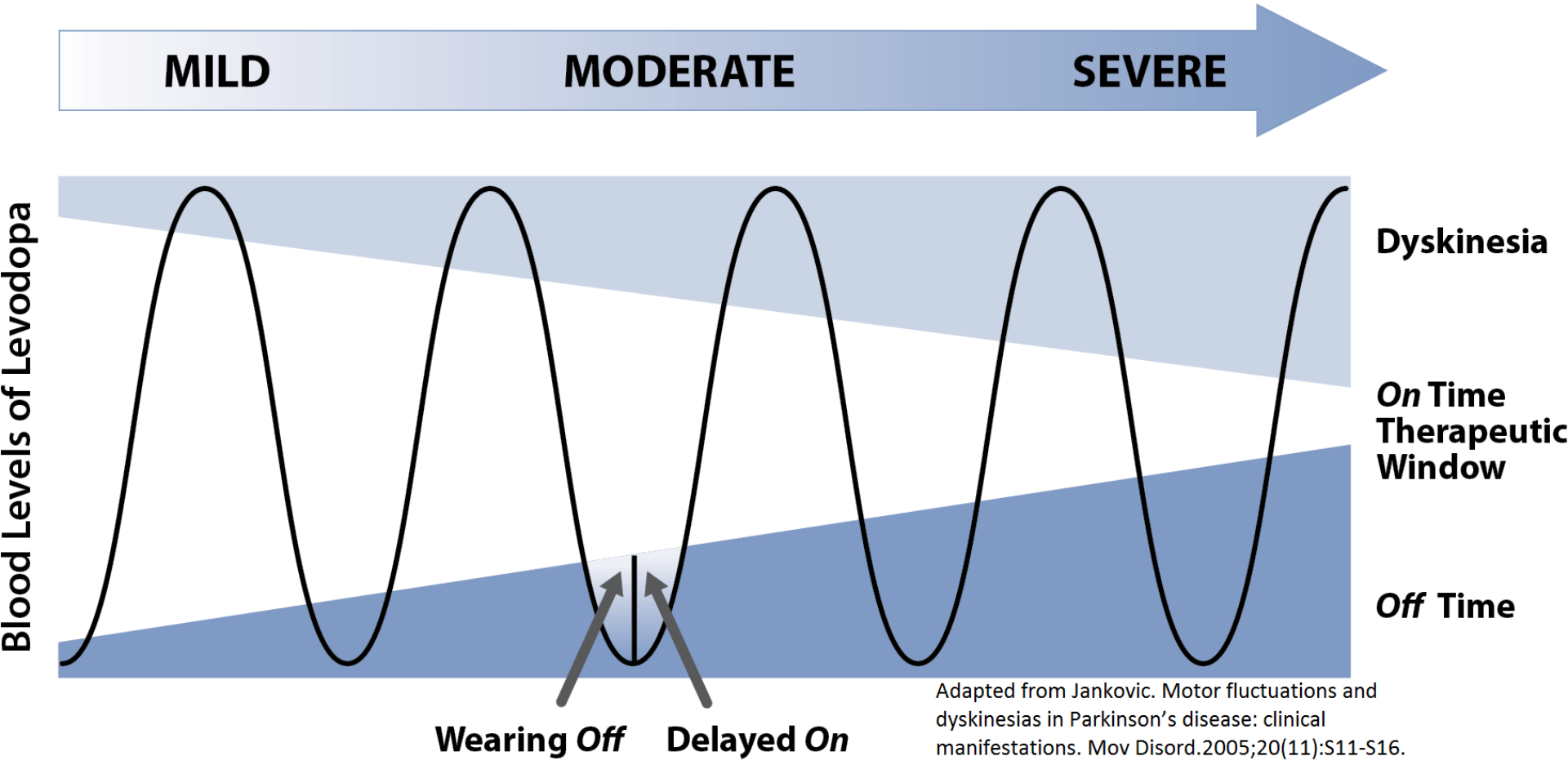
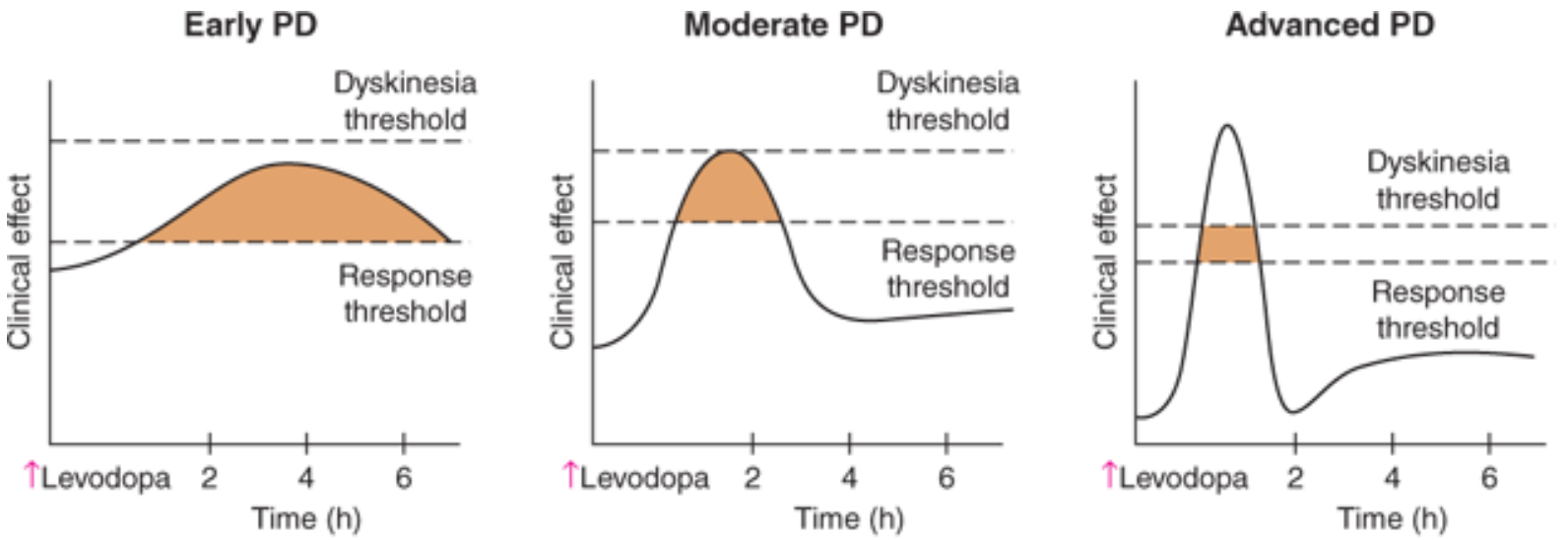


Adapted from Jankovic. Motor fluctuations and dyskinesias in Parkinson's disease: clinical manifestations. Mov Disord.2005;20(11):S11-S16.



- Long-duration motor response
- Low incidence of dyskinesias

- Short-duration motor response
- "On" time may be associated with dyskinesias

- Short-duration motor response
- "On" time consistently associated with dyskinesias

Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition.
www.accessmedicine.com
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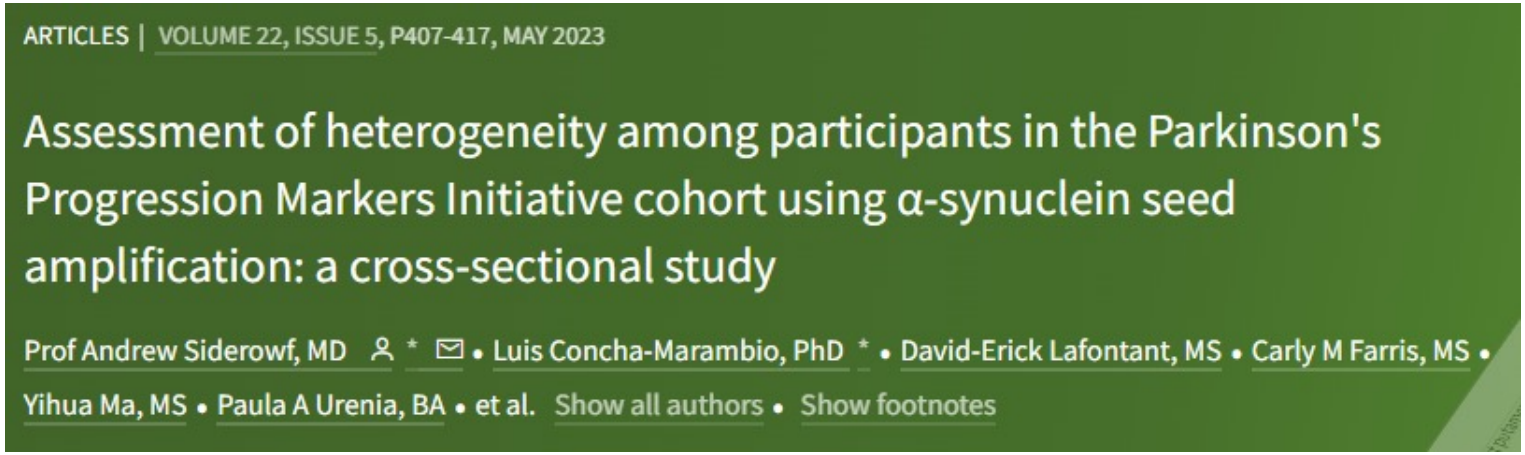
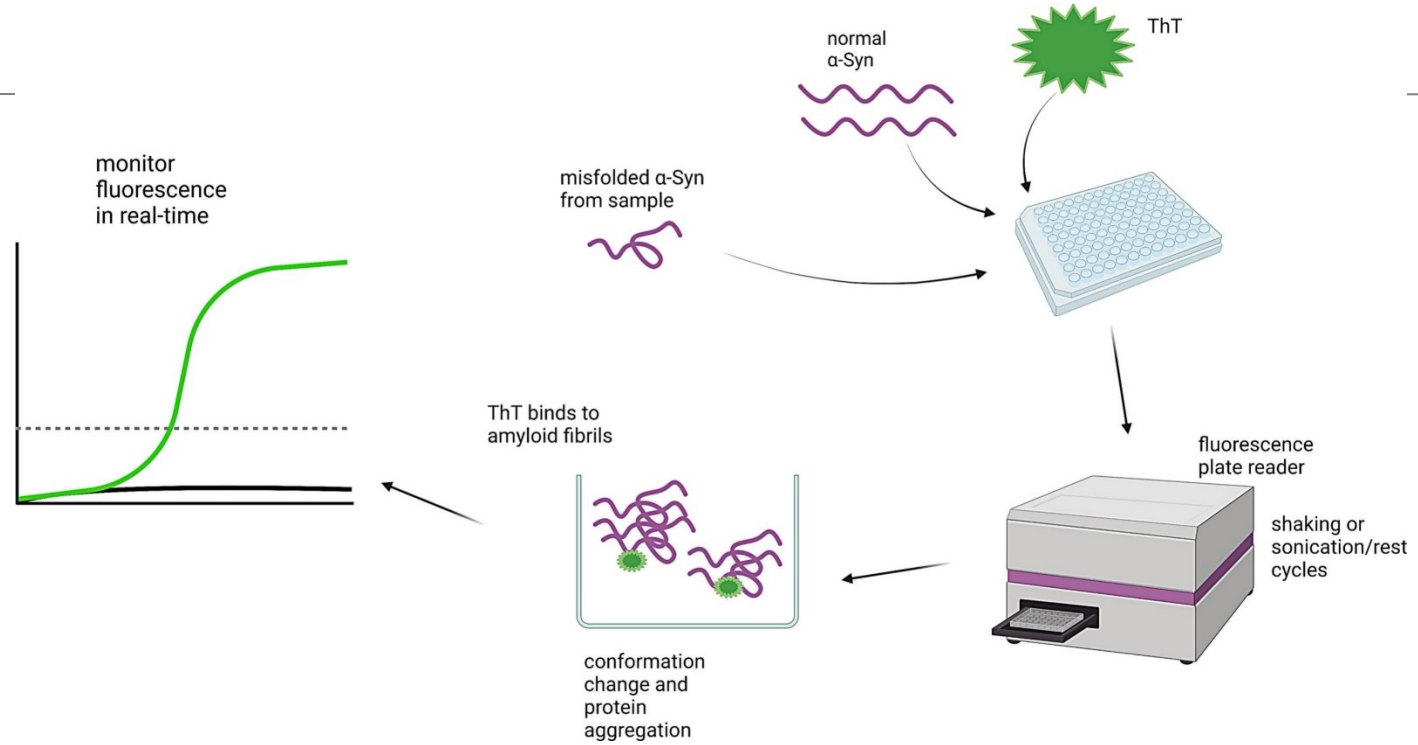
"I am deeply moved by this breakthrough and endlessly grateful to everyone who has endeavored to bring us this far."
— Michael J. Fox
Breaking News: Parkinson's Disease Biomarker Found
The Michael J. Fox Foundation has announced a significant breakthrough in the search for a Parkinson's biomarker.
Read More



- Seed amplification assay: designed to detect and measure the presence of abnormal alpha-synuclein protein
- "Seed" represents misfolded alpha-synuclein that initiates larger protein aggregates“
- "Amplification" refers to increasing the amount of misfolded proteins for easier detection



- Mix biological sample (e.g., cerebrospinal fluid, brain tissue) with normal alpha-synuclein proteins
- Misfolded "seeds" in the sample trigger misfolding and aggregation of normal proteins
- Process is repeated to significantly increase the number of misfolded proteins

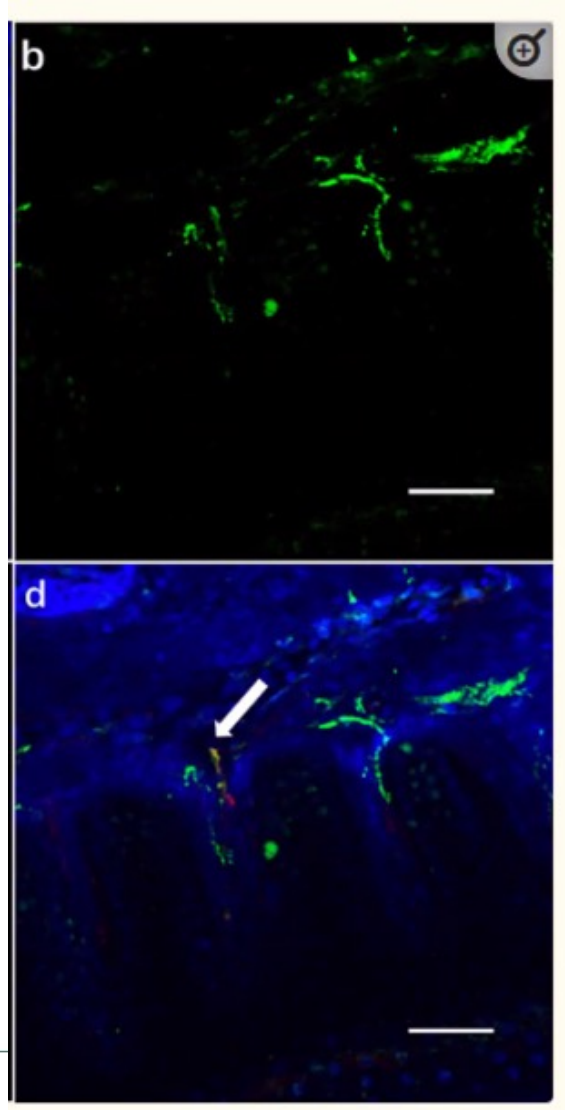
Kurapova, Chouliaras, O'Brien, The promise of amplification assays for accurate early detection of α-synucleinopathies: A review, Exp Ger, Vol 165, 2022.

α-synuclein seed amplification: a cross-sectional study of the PPMI

- PPMI: large registry of clinical and biomarker data: 33 clinical sites, 11 countries, 1,400 participants
- 1123 participants from 2010 to 2019: 545 with PD, 163 controls, 51 prodromal, 310 carriers
- Sensitivity for Parkinson's disease was 88%
- sensitivity in sporadic Parkinson's disease with typical olfactory deficit was 99%
- Lower in subgroups including LRRK2 Parkinson's disease at 68%
- sporadic Parkinson's disease without olfactory deficit at 78%
- LRRK2 variant and normal olfaction had an even lower α-synuclein SAA positivity rate 35%

Skin synuclein biopsy

- P-Alpha synuclein and Lewy Bodies in skin
- causes: seborrheic dermatitis, sweating dysfunction
- Findings: Loss of nerve fibers across layers of skin
- Frequency of deposits decreases as you move away from center of body
- Problems: Inconsistencies across studies, small sample sizes, most cross sectional
- Variable sensitivity, especially in patients w/o autonomic failure
- Low participation of early PD patients
- not covered by insurance
- Questions: Best technique, where, when



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What do we already have?

Medication choices

- Mainstays:
  - Dopamine
    - Levodopa: 1.5h half life
    - Other formulations: inhaled, long lasting
  - Dopamine agonists
    - Pramipexole, ropinirole, rotigotine
    - Other formulations: injectable, sublingual
- Add-ons
  - Extenders: rasagaline, entacapone, opicapone
  - Antidyskinetics: amantadine, gocovri
  - Anti-tremor: trihexyphenidyl

How do Parkinson' medications affect the progression of Parkinson's disease and the onset of new symptoms?

- medications are symptomatic.
- They do not have an impact on disease course.
- There are two caveats:
  - Being on medication can allow you to remain more active, which will slow progression
  - Being on medication can allow you to avoid falls

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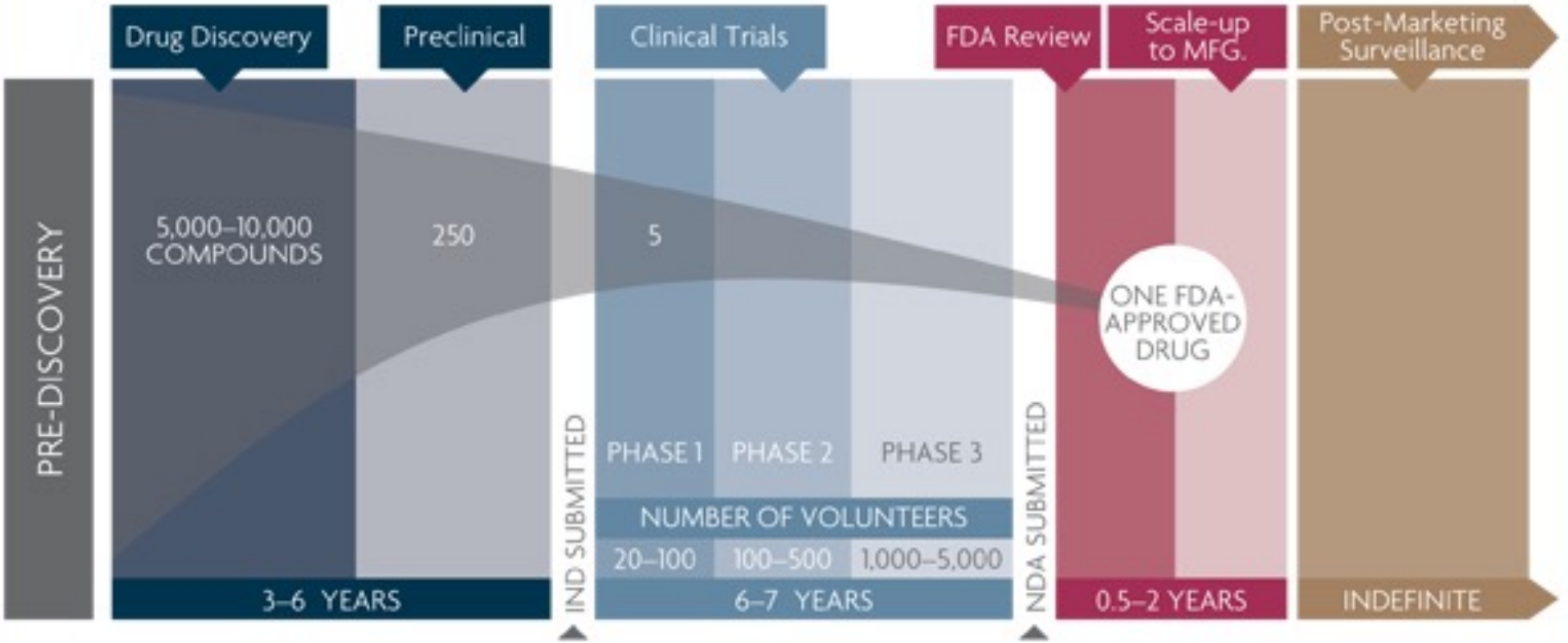
What's new?

The Research and Development Process

Developing a new medicine takes an average of 10–15 years.



Source: PhRMA®

Clinical Trials

- Phase I trials: test in a small group (20–80) *for the first time*.
- The purpose is to learn about safety and identify side effects.

Clinical Trials

- Phase II trials: The new drug or treatment is given to a larger group of people (100–300) to determine its *effectiveness* and dose, and to further study its safety.

Clinical Trials

- Phase III trials: The new treatment is given to large groups (1,000–3,000) to confirm effectiveness & dose, monitor side effects, and *compare it with standard treatments*

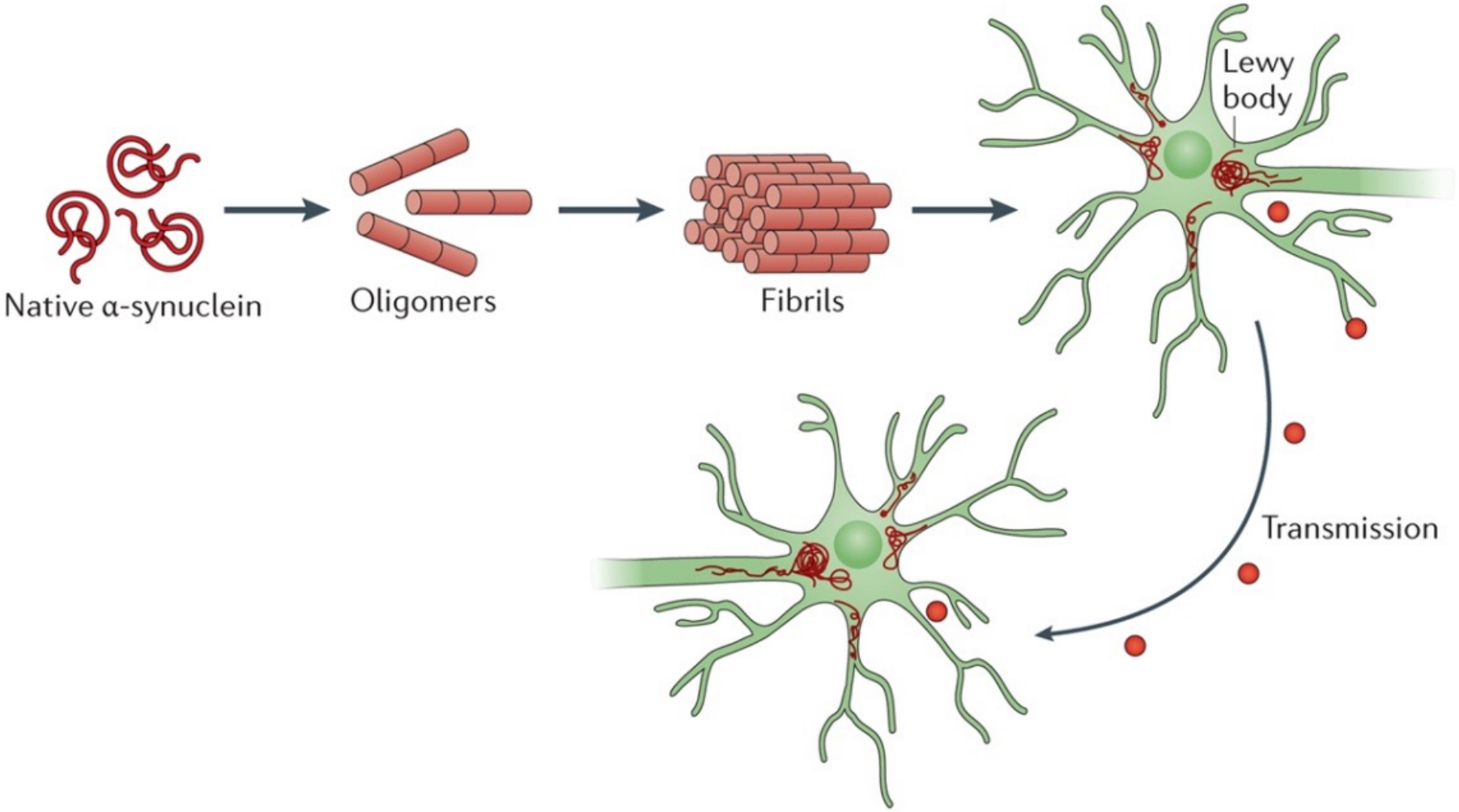
Clinical Trials

- Phase IV trials: After FDA approval researchers track its safety in the general population, seeking more information about treatment's benefits and optimal use.

Outline

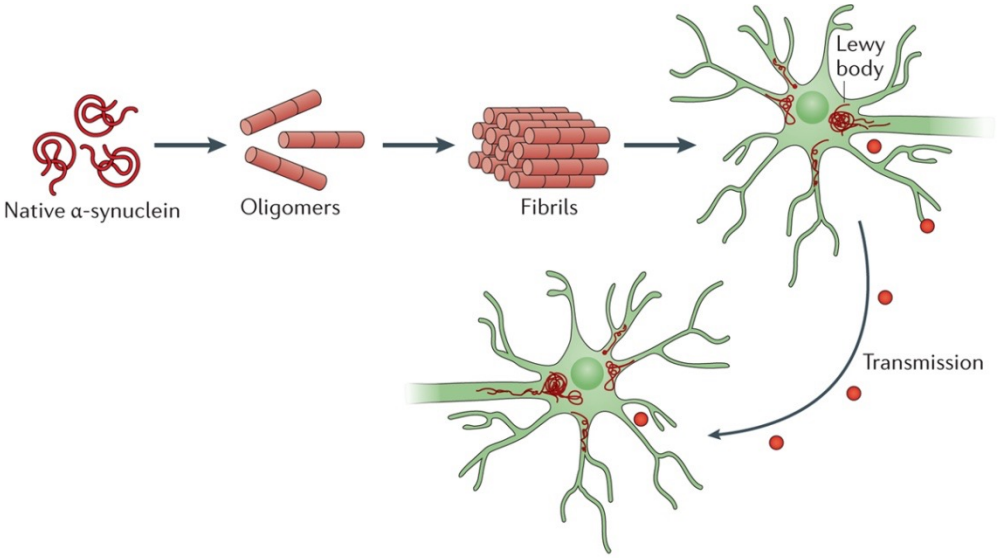
- **Disease modifying agents**
- Treatment of Early PD
- Treatment of Advanced PD
- Treatment of Non-motor PD symptoms

Alpha Synuclein target



Alpha Synuclein target

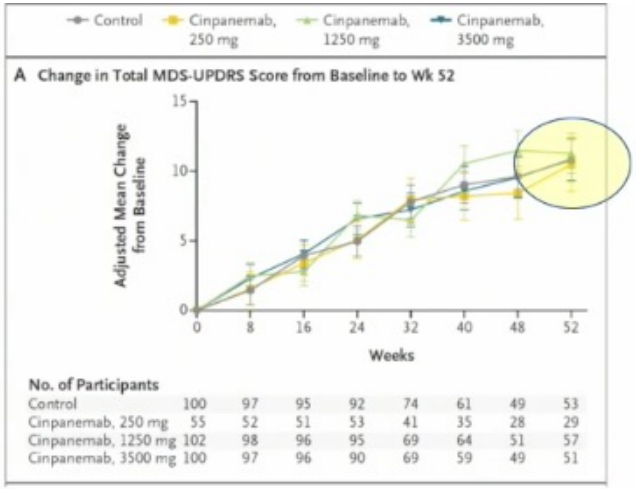
- Several strategies:
  - Immunize against synuclein
  - Prevent misfolding
  - Prevent aggregation
  - Promote synuclein breakdown

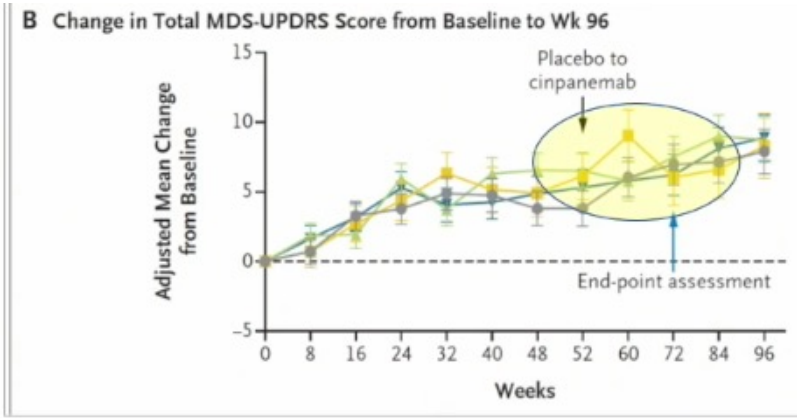


Alpha Synuclein target – Passive Immunization – SPARK STUDY

BIIB054 – Cinpanememab

- Human –derived monoclonal antibody that binds preferentially to aggregated synuclein
- Ph2, randomized, DB, PC
- Population: 357 PD patients (disease duration <3y), no antiPD treatment.
- Treatment: Randomization to escalating doses of Cinpanemab or placebo.
- Administered IV, every 4 weeks for 96 weeks.
- Primary outcome: MDS-UPDRS part I-II-III at 52 and 72 weeks.
- Failed primary end-point and no effect on secondary outcomes: DAT scan, QoL, ADLs).





No further development

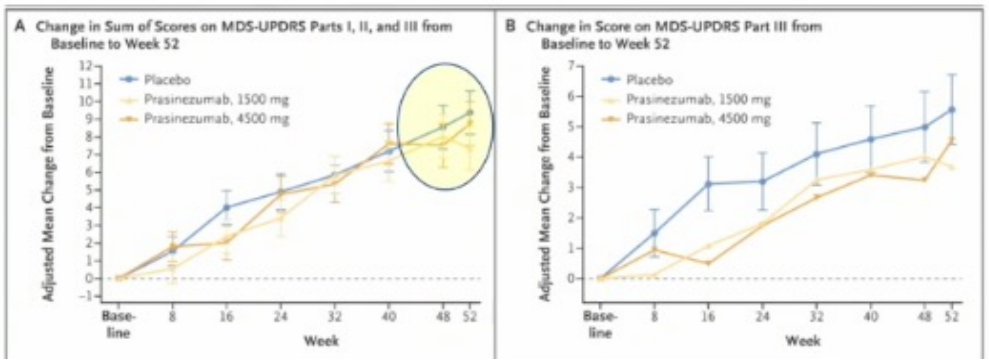
Lang et al. NEJM 2022

Alpha Synuclein target – Passive Immunization – PASADENA TRIAL

Prazinesumab (Ro7046015/PRX002)

- Binds synuclein with higher selectivity for fibrillar over monomeric forms.
- Ph2, randomized, DB, PC
- Population: 316 PD patients (disease duration <2y), de novo or MAOBI. Over 52 weeks plus second phase of 52 week blinded to dose for all patients.
- Primary endpoint: UPDRS part I-II-III
- Results: Primary endpoint not met at week 52.
- Early vs delayed start group with -2.17 (80% CI, 4.37, 0.03) at week 104 at the MDS-UPDRS III (no changes in DAT scan)
- Ongoing Phase 2b trial: randomized placebo/control: PADOVA

AE: infusion reaction, nausea, headache, rash (19%-34%-16% for 1500mg, 4500mg and placebo)



1.9 (-3.5;0.9) points

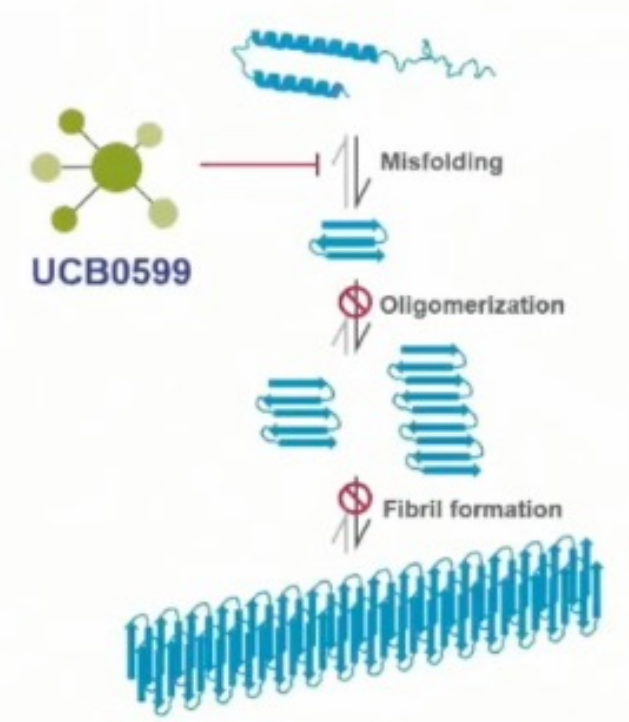
Pagano et al. NEJM 2022

Alpha Synuclein target – Inhibition of AS misfolding

UCB0599

- Oral, small molecule, brain penetrant
- Ph1b, randomized, DB, PC
- 21 PD patients and 73 HC at 180 and 360
  Primary outcome: safety and tolerability
  Results: Acceptable safety/tolerability profile and predictable PK
- CSF: Linear increase with increasing dosing.

- Phase 2 ongoing (NCT04658186): ORCHESTRA STUDY
- Enrollment complete

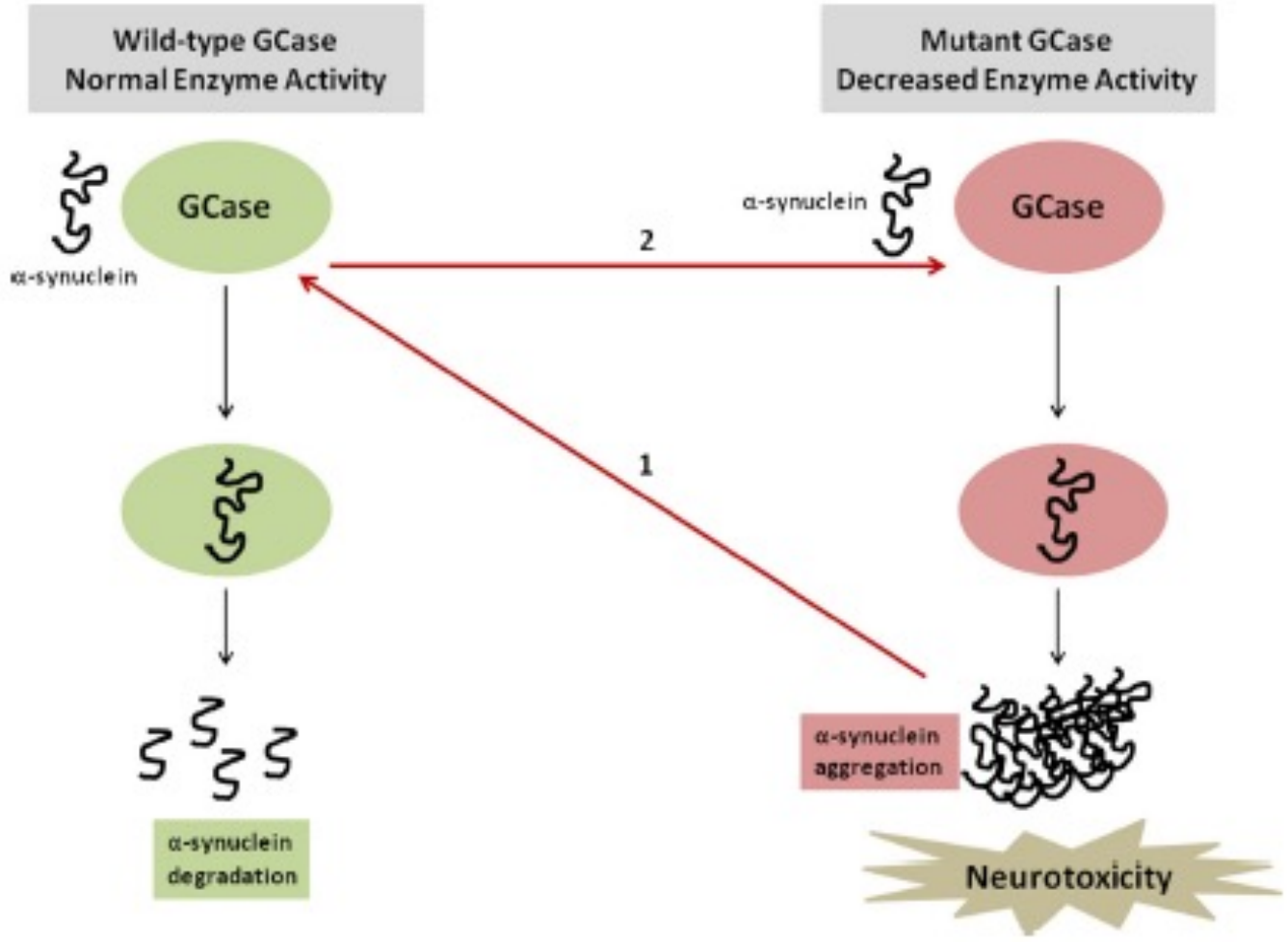


Alpha Synuclein target

- Several strategies:
  - Immunize against synuclein
    - Cinpanemab (SPARK, closed)
    - Prazinesumab (PADOVA, ongoing)
  - Prevent misfolding
    - UCB7853 (ORCHESTRA, ongoing)
  - Prevent aggregation
    - Anle138b (ongoing, UK)
  - Promote synuclein breakdown
    - IKT-148009 (Inhibikase, ongoing)

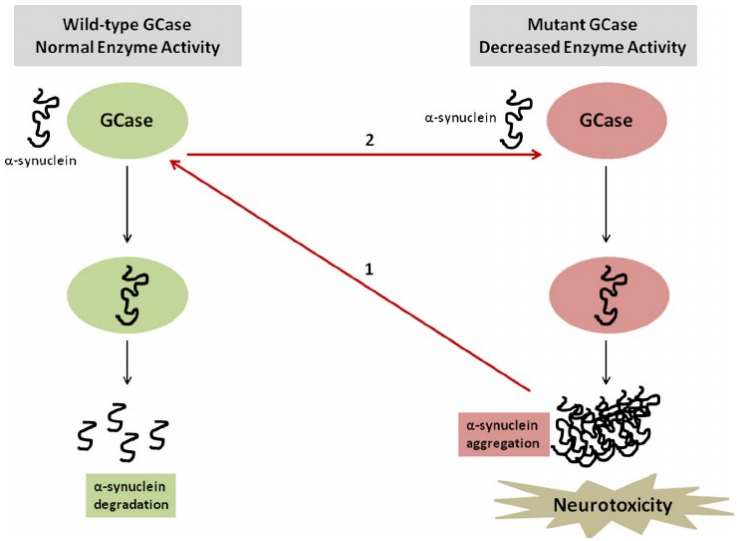
Modifying Glucocerebrosidase (GBA)

Fig. 2 Overview of possible mechanisms underlying GBA-associated PD. Under physiological conditions, wild-type GCase interacts with α-synuclein, forcing α-synuclein degradation (green). In a bidirectional pathogenic loop, functional loss of GCase (e.g., due to *GBA* mutations) compromises lysosomal α-synuclein degradation, causes accumulation of α-synuclein, and results in neurotoxicity through aggregation-dependent mechanisms on the one hand while aggregated α-synuclein inhibits the lysosomal activity of normal GCase in PD patients on the other hand (red)



Modifying Glucocerebrosidase (GBA)

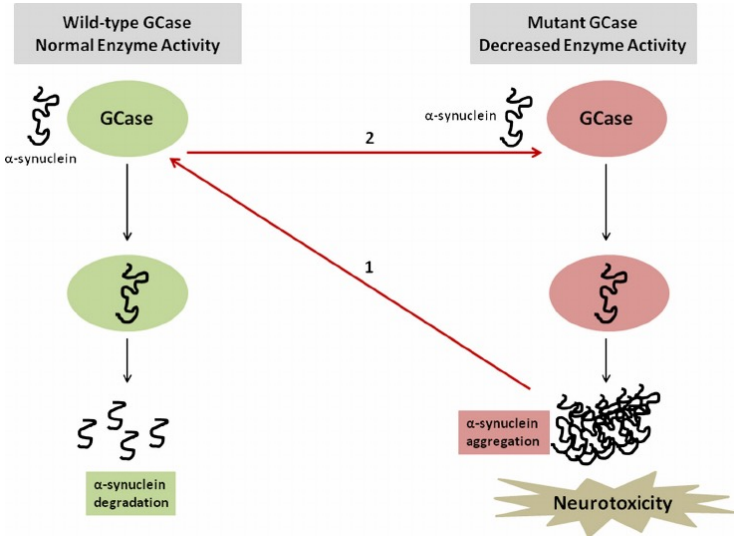
- Roughly speaking, decreased GBA function means greater alpha-synuclein levels
- Glucocerebrosidase (GBA) is an enzyme that converts glucosylceramide to glucose
- Glu-Cer >>Gcase/GBA (lysosome) >> Ceramide + Glu
- GBA mutations are present in 3 to 30% of patients with PD
- Modifying GBA activity could help people with
  - PD + GBA mutation
  - Sporadic PD with low GBA activity



1.Sardi SP et al. Proc Natl Acad Sci U S A 2017;114:2699-2704
2.McNeil A, et al. Brain 2014;137:1481-1495

Modifying Glucocerebrosidase (GBA)

- Strategies:
  - Glu-Cer >>Gcase/GBA (lysosome) >> Ceramide + Glu
  - Block Glucosyl ceramide formation
    - Venglustat: MOVES-PD
  - Increase GBA function
    - ambroxol: AMBITIOUS
  - Gene therapy
    - AAV9-GBA1 gene: PROPEL



1.Sardi SP et al. Proc Natl Acad Sci U S A 2017;114:2699-2704
2.McNeil A, et al. Brain 2014;137:1481-1495

Glucocerebrosidase specific

Venglustat

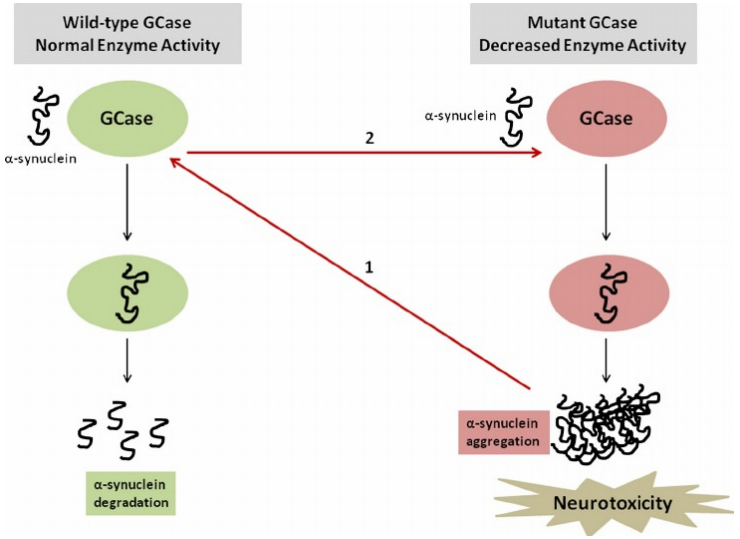
- Glucosylceramide synthase inhibitor.
- Blocks formation of Glu-Cer, GL-1. Excess GL-1 levels accelerate and stabilize formation of toxic AS oligomers.
- Enhance lysosomal or proteasomal enzyme activity to promote clearance of intracellular AS.

MOVES PD STUDY

- **Ph2 (NCT02906020) (Gregg et al, Neurology Dis 2022)**
- 273 patients, early PD carrying het GBA mutation or other pre-specified variant
- Ph2, multicenter, randomized, DB, PC, to assess the efficacy, safety, PK and pharmacodynamics of GZ/SAR40267
- Results: Not met primary endpoint (MDS-UPDRS II-III)

Modifying Glucocerebrosidase (GBA)

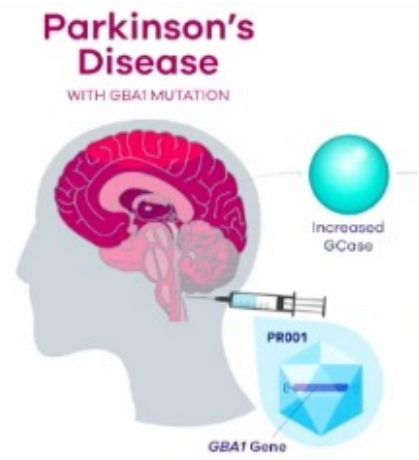
- Phase 2 trial with ambroxol: AMBITIOUS
  - increases GCase activity in preclinical models (cell lines)
  - 60 patients with PD and GBA mutations
  - 2022-24, in Italy



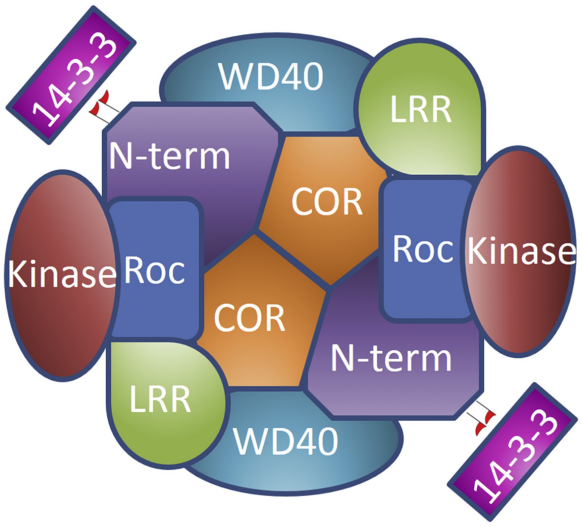
Glucocerebrosidase specific

PROPEL STUDY (B-glucocerebrosidase gene therapy)

- Ph1/2a ongoing, open label, high or low dose of single intra-cisternal magna administration of AAV9-GBA1 gene
- Follow up: Up to 5y
- First in human administration
- 24 PD patients with at least 1 GBA mutation
- Ongoing



LRRK2



LRRK2 dimer

- Mutation LRRK2 in PD: Toxic gain of function
- Increase kinase activity: kinases add phosphate signals to molecules
- Inhibition of LRRK2 kinase activity: Neuroprotective

- Denali Therapeutics: DNL201
- DNL201 reduced phosphorylation of LRRK2 and demonstrated improved lysosomal function in cellular models of disease
- phase 1 and phase 1b clinical trials (122 healthy volunteers, 28 patients with PD)
  - inhibited LRRK2
  - well tolerated
  - demonstrated alteration of downstream lysosomal biomarkers

West AB. Exp Neurol 2017;298:236-245

Insulin Resistance

Agonists of the glucagon-like peptide-1 (GLP-1) receptor

- Increase transcription of tyrosine hydroxylase, activation of the transcription factor cyclic adenosine monophosphate response element binding protein, implicated in neuronal survival and synaptic activity
- GLP-1 treatment: lower incidence of PD in DM2 patients. DM2 have faster progression (Athauda MDJ 2022)
- Exenatide 2 mg SQ: -3.5 points vs PLA at MDS-UPDRS III (Athauda et al, Lancet 2017)

EXENATIDE PD3 STUDY (NCT04232969) – NLY01

Ph3 ongoing. Randomized, PC, DB, 194 patients, HY <2.5, over 48 weeks, 2mg ER SQ
Primary endpoint: MDS-UPDRS III (OFF)
Estimated study completion: 2024
Ph2 ongoing on 255 early PD patients with 2.5 or 5 mg SQ over 36 weeks
Results: Pending

LIRAGLUTIDE (NCT02953665). Bresee et al. MDS abstract 2022, P790.

Ph2, concluded. Randomized PC, DB.
63 PD with disease duration >2y, over 54 weeks, 1.8 mg SQ
Primary endpoint: NMSS, MDS-UPDRS Part III, MDRS2
Results: Improvement NMSS $p<0.05$ + PDQ39, MDS-UPDRS II

Insulin Resistance

Agonists of the glucagon-like peptide-1 (GLP-1) receptor

- Increase transcription of tyrosine hydroxylase, activation of the transcription factor cyclic adenosine monophosphate response element binding protein, implicated in neuronal survival and synaptic activity
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LIXIPARK STUDY, Lixisenatide (NCT03439943)

Ph2, parallel groups, 2 arms, randomized, PC, DB, proof of concept
Completed Dec 2021
Primary endpoint: MDS-UPDRS III
Results: Pending

GIPD STUDY, Semaglutide (NCT03659682)

Ph2 ongoing. Single center, DB, randomized
126 PD patients, disease duration <1y, over 48 months
Primary endpoint: MDS-UPDRS III (OFF state)
Results: Pending

Outline

- Disease modifying agents
- **Treatment of Early PD**
- Treatment of Advanced PD
- Treatment of Non-motor PD symptoms

Treatment of Early-Stage PD

Concluded

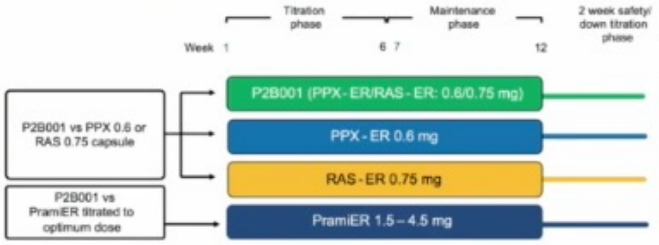
- **P2B001** (low dose of ER pramipexole and rasagiline)
- **Amantadine**, NMDA glutamate receptor antagonist, **PREMANDYSK STUDY**
- **Exercise**: aerobic exercise, Long-term TAI-CHI, brisk walking, virtual reality

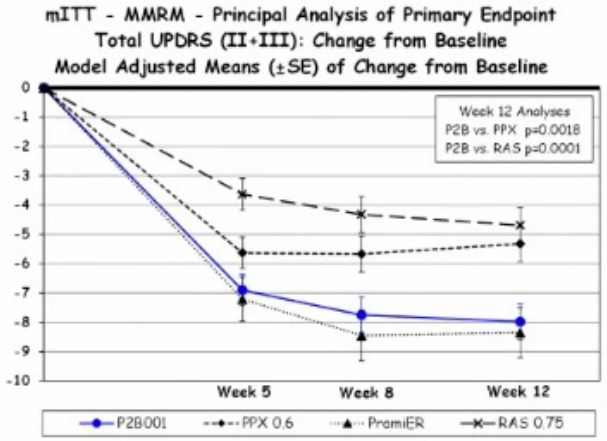
On-going/Just Concluded

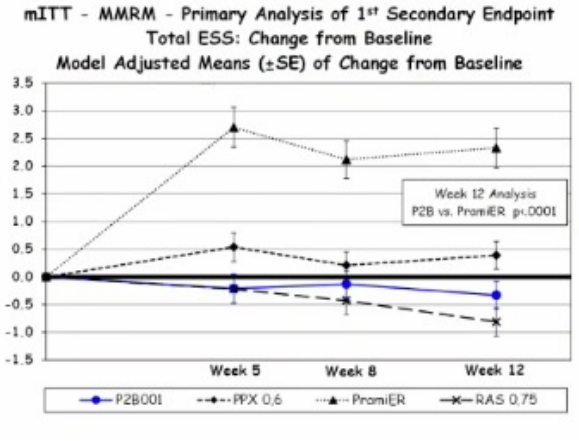
- **TAVAPADON** (partial dopamine D1 and D5 receptor agonist) **TEMPO-1/-2 STUDY**
- **Opicapone**, COMT-I, **EPSILON STUDY**
- **Exercise**: aerobic exercise, treadmill walking, In-home Cycling, smart-phone based exercise

Treatment of Early-Stage PD

- ✓ **P2B001 (low dose of ER pramipexole and rasagiline; Hauser et al., Adv Ther 2022 & AAN Congress Abstract 2022**, NCT03329508; ***Olanow et al., MDS Abstract 2022*)**: **Phase 3**, randomized, DB, parallel group
- **525 Untreated PD** patients (disease duration < 3 years)



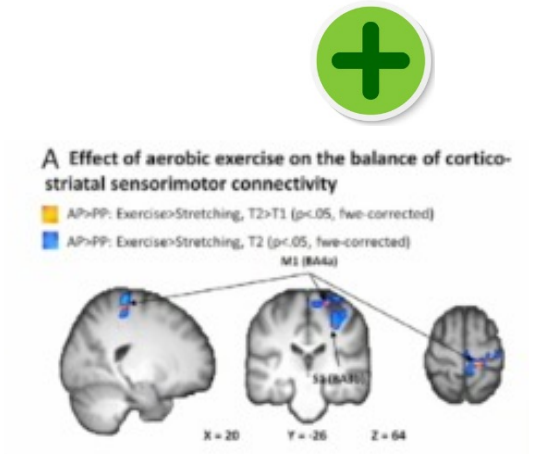


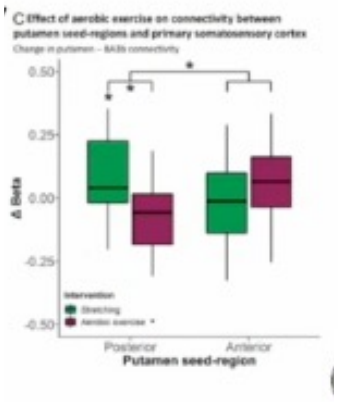


Treatment of Early-Stage PD - Exercise

Subgroup of Park in Shape Trial: Jahanson et al, JAMA Neurol 2022

- Randomized, DB (without specifying that one of the programs was considered a control intervention), controlled
- Groups: Aerobic exercise (stationary home trainer, 50-80% HR reserve) vs stretching
- 56 early PD
- Over 6 months
- Intervention: 3 times per week x 3—45 min
- Primary outcome: Cerebral changes in resting state functional and structural MRI, oculo-motor cognitive tasks
- Results: Aerobic exercise, led to increased functional connectivity of the anterior putamen with sensory motor cortex relative to posterior putamen. In addition, lowered changes in brain atrophy (improve preservation of cortico-striatal sensory motor network).





PARK-in-SHAPE trial (Van der Kolk et al, Lancet 2019
-4.2 at MDS UPDRS III in meds OFF (aerobic exercise vs stretching)

Treatment of Early-Stage PD - Exercise

LONG TERM TAI-CHI – Li et al. Translational Neurodegeneration 2022
95 early PD
Randomized to: Tai-chi (N=32), brisk walking (N=31) and no exercise (N=32), over 12 months
Results: Statistically improvement of BS (Berg scale) and TUG, significantly better at 6 and 12 months in TAI-CHI group. ($p<0.005$; $p<0.0012$)
Retention rate: 32/32 TAI-CHI, 17/31 brisk walking and 17/32 control group

BRISK WALKING - Mak et al, Journal of Parkinson Disease 2021
70 PD patients, disease duration <5y
Randomized to brisk walking and balance exercise (BW) vs upper limb training group (CON), over 6 months
Primary outcome: MDS-UPDRS III (ON), TUG secondary
Results: BW group showed greater significant decreases from baseline than CON group in UPDRS III (-6.0 vs -1.4, $p<0.001$) and TUG time ($p<0.01$)

Treatment of Early-Stage PD - Exercise

ON-GOING

SPARX3 STUDY – Treadmill walking (NCT04284436)
Ongoing, multicenter, randomized, single blind
Endurance treadmill exercise to 65% HR vs 85% HR, 4 times/w, 12 months
370 PD, no treatment, age 40-80
Primary outcome: MDS-UPDRS III

LTSE-PD STUDY - Aerobic exercise in PD (NCT 13808675)
One year, single-blind, parallel, group, randomized, controlled.
Compares the effects of moderate aerobic exercise (50 min x 3/w) vs usual care + health education
100 PD, HY 1-3
Primary outcome: MDS-UPDRS, med OFF

Long term Effects of combined balance and brisk walking (150 min/w) in PD (NCT 04665869)
Balance and brisk walking vs strengthening exercise, over 6-12 months
77 PD, HT 2-3
Primary outcome: MDS-UPDRS I and III

Outline

- Disease modifying agents
- Treatment of Early PD
- **Treatment of Advanced PD**
- Treatment of Non-motor PD symptoms

Treatment of Advanced PD: Recent and ongoing studies

Motor fluctuations

Concluded

- **Foliglurax,** Positive allosteric modulator of the mGlu4R
- **Istradefylline**, adenosine A_{2A} receptor antagonist ***(MDS Abstract, P724), ISTRA ADJUST PD***
- **IPX203**, ER L-dopa/CD ***(MDS Abstract, P725), RISE-PD***
- **KW-6356**, selective adenosine A2A receptor antagonist/inverse agonist ***(MDS Abstract, P743)***
- **Subcutaneous Foslevodopa/Foscarbidopa** ***(MDS Abstract, P775)***
- **Subcutaneous night-time only apomorphine infusion,** dopamine agonist D2,D3 and D5 receptor
- **SC-Apomorphine vs. SL apomorphine** ***(MDS Abstract, P760/769)***

On-going

Motor fluctuations

- **Tavapadon**, dopamine D1/D5 agonist (Phase 3) –**TEMPO 3 STUDY**
- **Bumetanide –**Sodium/potassium/chloride cotransporter isoform 1 antagonist (Phase 2) **CUREPARK STUDY**
- **CVN424 -**selective and novel GPR6 inverse agonist (Phase 2)

Dyskinesia

Concluded

- **IR/ER amantadine OS320**
- **Levodopa-Carbidopa Intestinal Gel**
- **Transcranial static magnetic field stimulation**

On-going

- **Mesdopetam** (dopamine D3-receptor antagonist) (Phase 2b)
- **AV-101** (L-4-chlorokynurenine / inhibits the glycine co-agonist site of NMDA receptors) (Phase 2)
- **NLX-112: 5HT1A agonist**
- **JM-010** buspirone combined (**5HT1A** partial agonist) with zolmitriptan (**5HT1B/1D agonist**) (Phase 2)
- **Dipraglurant**, negative allosteric modulator of the mGlu5 receptor (Phase 2/3)

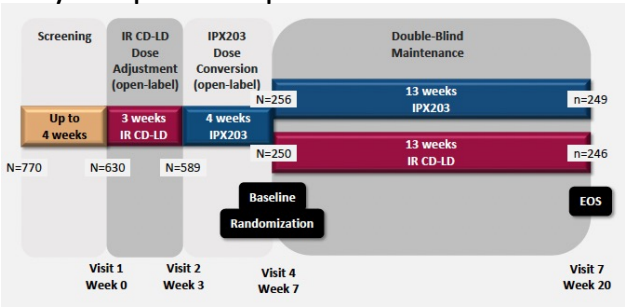
OTHERS

- **Gene therapy**: NBIb-1817 (Phase1b)

IPX203: Sponsor submitted information to FDA. Final decision before 6/30/23.

Motor fluctuations: IPX203 (RISE PD Trial)

Ph3, RCT, DB
IPX203: ER + IR CD/LD
Advanced PD >2.5hr OFF/day
1ry endpoint: Improvement in GOOD On time



RESULTS

IPX203: 0.53 hr more GOOD ON time, -0.48hr less OFF time, better PGIC (29.7 vs 18.8 very much or much improved. No changes in UPDRS 3 scores. (p=0.0194)
Dosing: 3/day vs 5/day

POST-HOC

IPX203 increased good ON time by 1.55 hr per dose (3.76hr vs 2.21) c/w IR CD/LD. (p<0.0001)

Table 1. RISE-PD efficacy results: Primary and key secondary endpoints

	Week 0 Enrollment	Week 7 Baseline (Randomization)	Week 20 End of Study (or Early Termination)	p-value
Mean "Good On" time (h)				
IPX-203	9.46	11.67	11.35	
immediate-release CD/LD	9.61	11.72	10.77	0.0194Δ
Mean "Off" time (h)				
IPX-203	6.15	3.95	4.18	
immediate-release CD/LD	6.05	4.02	4.75	0.0252Δ
Percentage of patients who reported "much improved" or "very much improved" scores on the PGI-C scale				
IPX-203	N/A	N/A	29.7%	
immediate-release CD/LD	N/A	N/A	18.8%	0.0015□
Mean MDS-UPDRS part III score				
IPX-203	29.6	26.9	27.8	
immediate-release CD/LD	29.7	27.0	28.0	0.9587Δ
Mean MDS-UPDRS Sum of part II + III score				
IPX-203	42.9	38.9	40.6	
immediate-release CD/LD	42.9	39.3	41.1	0.9668Δ

Δ = p-value based on change from Week 7 (Baseline) to Week 20 (End of Study or Early Termination [EOS/ET])
□ = p-value based on comparison of treatments at Week 20 (EOS/ET)

1. Hauser RA, Espay AJ, LeWitt P, et al. A Phase 3 Trial of IPX203 vs CD-LD IR in Parkinson's Disease Patients with Motor Fluctuations (RISE-PD). Presented at: AAN Annual Meeting; April 2-7, 2022; Seattle, WA, and virtual. Abstract 001225.
2. Hauser RA, Fernandez HH, Klos K, et al. Duration of Benefit Per Dose: Post Hoc Analysis of "Good On" Time Per Dose for IPX203 vs CD-LD IR in the RISE-PD Phase 3 Trial. Presented at: AAN Annual Meeting; April 2-7, 2022; Seattle, WA, and virtual. Abstract 001231.

Motor fluctuations: Subcutaneous Foslevodopa/Foscarbidopa 24hr/d

Randomized, DB, double-dummy, active-controlled, Ph3 trial

Randomized 1:1 to fLD/fCD (prodrug) 24hr/day infusion (SQ pump) versus oral CD/LD over 12 weeks
74 patients fCD/fLD; 67 patients oral CD/LD

144 PD patients with 2.5 hr motor fluctuations
65 academic centers in USA and Australia

Primary outcome: ON time w/o troublesome dyskinesia

Results
Increment of good ON of 1.75 hr/day (2.72 vs 0.97, 95% CI 0.46 to 3.05; p=0.0083 vs CD/LD (and OFF time -1.79 hrs; 2.75 vs 0.96; (95% CI -3.03 to -0.54)

Adverse Events

85% fCD/fLD, 63% oral CD/LD (SAE: 8 vs 6%)
Infusion site AE: erythema 27%, pain 26%, cellulitis 19%, edema 12%).
Premature d/c study: 22% (fCD/fLD) vs 1% (oral CD/LD
Psychosis: 15% (fCD/fLD) vs 3% (oral CD/LD) >>> nocturnal CD/LD?

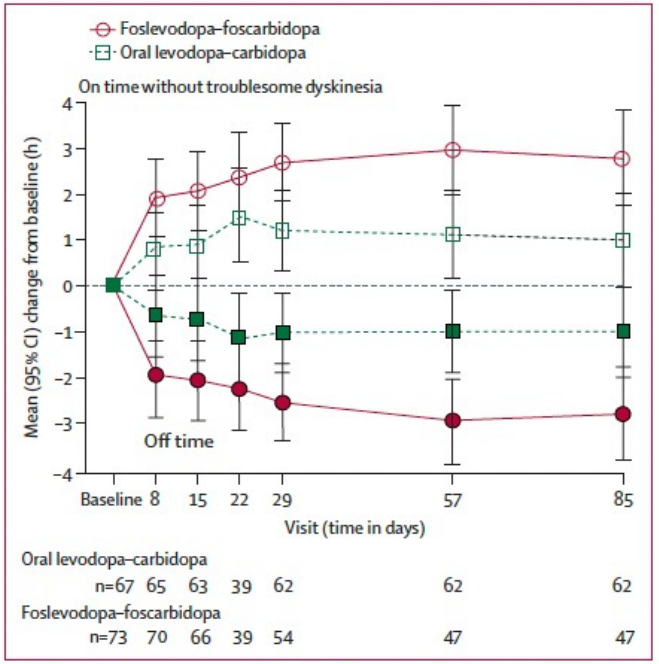


Figure 2: **Least squares mean (95% CI) of change from baseline in average daily on time without troublesome dyskinesia and off time (full analysis set)**
Assessed using a 24-h Parkinson's disease diary and normalised to a 16-h waking day. On time without troublesome dyskinesia is the sum of on time without dyskinesia and on time with non-troublesome dyskinesia. Error bars represent the 95% CI of the least squares mean change from baseline. Day 22 was an optional visit at the investigator's discretion and based on the participant's Parkinson's disease symptoms.

M Soileau, et al. Lancet Neurol 2022;21:1099

Gene Therapy

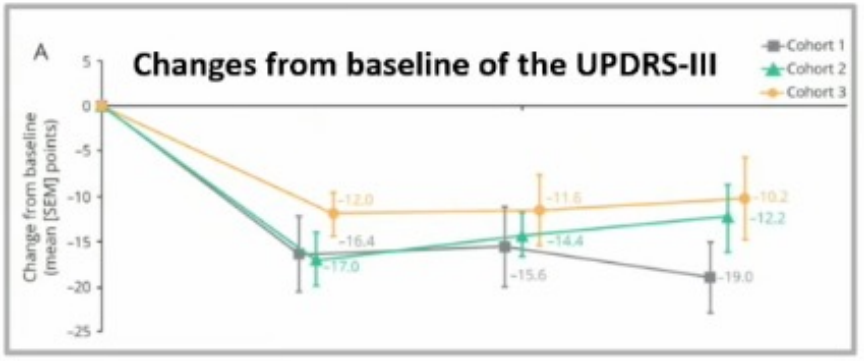
NBIb-1817
Phase 1b, open label, escalation trial
AAV2 gene therapy encoding L-AADC, 3 doses
15 patients advanced PD with motor fluctuations, HY >=2.5 in OFF time and disease duration >5y, over 36 months

Procedure: Intraoperative MRI-guided putaminal infusions

Primary outcome: safety and tolerability

Secondary outcomes: LED reduction, motor fluctuations/dyskinesia diary, UDysRS, UPDRS III OFF, PDQ39, CGI-I

Results
No vector-related SAEs reported. TEAEs were mostly transient, including headache (11/15) and dyskinesias (4/15)
22-30% reduction in LED in higher cohort doses and global improvement of UPDRS III OFF scores at 36 months.
Heterogeneous data for PDQ39.



Class IV evidence that VY-AADC01 and the associated surgical delivery procedure were well-tolerated in a population 40–70 years of age with moderately advanced PD

Chadwick et al, Neurology Jan 2022

Stem Cell Therapy

- Bluerock therapeutics (phase 1, 2)
  - MSK-DA01 Cell Therapy: phase 1 – 12 patients
  - surgical transplantation of the dopamine-producing cells into the putamen.
  - Subjects then take medicines to partially suppress their immune system (aimed to prevent the body from rejecting the cells) for 1 year.
  - Assessed for 2 years post-transplant.

Focus ultrasound Sub-thalamotomy for PD

Randomized Trial of Focused Ultrasound Subthalamotomy for Parkinson's Disease

R. Martínez-Fernández, J.U. Máñez-Miró, R. Rodríguez-Rojas, M. del Álamo, B.B. Shah, F. Hernández-Fernández, J.A. Pineda-Pardo, M.H.G. Monje, B. Fernández-Rodríguez, S.A. Sperling, D. Mata-Marín, P. Guida, F. Alonso-Frech, I. Obeso, C. Gasca-Salas, L. Vela-Desojo, W.J. Elias, and J.A. Obeso

NEJM 2020

Conclusion: Focused ultrasound subthalamotomy in one hemisphere improved motor features of Parkinson's disease in selected patients with asymmetric signs.

Adverse events included speech (56%) and gait disturbances (48%), weakness on the treated side (22%), and dyskinesia in the OFF condition (19%). Tapered during the study period.

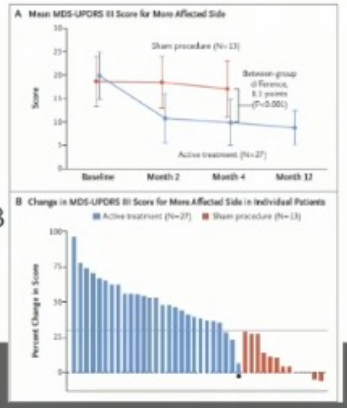
77 pts, 27 subthalamotomy/ 13 sham

Mean disease duration 6.2 years

Mean age 57.1 (35-74)

Mean MDS-UPDRS III: 39.9 OFF, 26.3

Mean LEDD 777.9 mg



Deuschl G et al, Mov disord 2022

Focus ultrasound Sub-thalamotomy for PD

Randomized Trial of Focused Ultrasound Subthalamotomy for Parkinson's Disease

R. Martínez-Fernández, J.U. Máñez-Miró, R. Rodríguez-Rojas, M. del Álamo, B.B. Shah, F. Hernández-Fernández, J.A. Pineda-Pardo, M.H.G. Monje, B. Fernández-Rodríguez, S.A. Sperling, D. Mata-Marín, P. Guida, F. Alonso-Frech, I. Obeso, C. Gasca-Salas, L. Vela-Desojo, W.J. Elias, and J.A. Obeso

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…es (48%), weakness on the treated side …d during the study period.

		Advanced PD with resistant fluctuations	Early PD with early fluctua-tions	Early PD without fluctua-tions	PD with treatment refractory tremor	PD with predominant unilateral symptoms
Non-lesional	DBS of the subthalamic nucleus					
	DBS of the globus pallidum internum					
	L-dopa/Carbidopa intestinal gel infusion					
	Apomorphine infusion					
lesional	Radiofrequency pallidotomy					
	Radiofrequency thalamotomy					
	Radiofrequency lesioning of subthalamic nucleus					
	Radiosurgery (Vim, Gpi, STN)					
	MRg-focused ultrasound					

with incision / incisionless / parenteral

Offer to elegible patients (e.p.) — Consider offering to e.p. — Consider offering to e.p. with strong limitations — Do not offer — Not applicable or no studies

Clinical practise statements: not recommended — or with limitations — Details: see text

Recommendation 8: Consider using unilateral MRgFUS of the STN in people with distinctly unilateral PD only within clinical studies or registries due to the limited data on this new treatment (16 voters, 100%).

Deuschl G et al, Mov disord 2022

REGION

Non-pharmacological - Freezing of Gait

Multitarget Transcranial Magnetic Stimulation
DB, randomized
77 PD with FOG
Randomized to tDCS vs sham stimulation of the L dorsolateral prefrontal cortex and primary motor cortex (M1)
10 sessions over 2 weeks and 5 sessions once a week

Primary outcome: FOG-provoking test performance in MED ON

Results: Failed (only improvement of 58% vs 35% patients at Likert scale, secondary outcome

Ongoing Trials on Gait and Balance

PHARMACOLOGICAL

CHIEF PD: Cholinesterase inhibitor to prevent falls in PD - NCT04226248
Ph3 randomized, PC, over 12 months
600 patients
Rivastigmine transdermal
HY 1-4, ambulatory but falling
Primary outcome: Fall rate

TAME PD

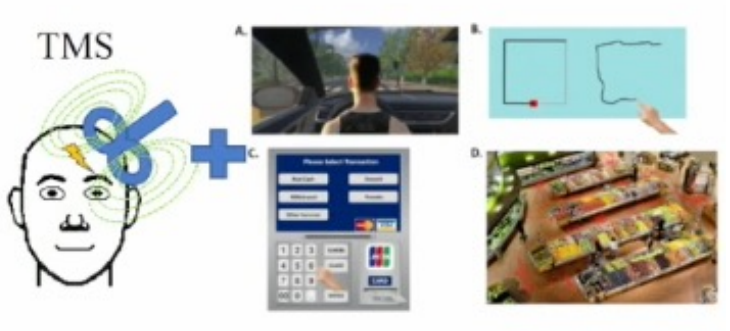
Physical Therapy, Atomoxetine and Methylphenidate to enhance Gait and Balance – NCR02879136
Pilot, Ph1, single center, rater blind, prospective randomized trial, 2 arm parallel group
HY 2-4, over 12 weeks
42 patients
Primary outcome: balance

Outline

- Disease modifying agents
- Treatment of Early PD
- Treatment of Advanced PD
- **Treatment of Non-motor PD symptoms**

Non-pharmacological - MCI

Virtual Reality (VR) and Repetitive transcranial Magnetic Stimulation (rTMS)
Randomized, controlled, single-blinded study
VR + rTMS vs rTMS vs sham
40 patients with MCI over 3 months



Primary outcome: Repeatable Battery for the assessment of Neuropsychological Status (RBANS)

Results:
rTMS-VR group exhibited significantly more improvements in total and delayed memory scores of the RBANS and the visuospatial/executive function score of the MoCA after intervention (p=0.0000-0.0046) and the delayed memory score of the BRANS (p=0.0028)

Ongoing Trials on Gait and Balance

PHARMACOLOGICAL

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Ph3 randomized, PC, over 12 months
600 patients
Rivastigmine transdermal
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HY 2-4, over 12 weeks
42 patients
Primary outcome: balance

Outline

- Overview of PD
- Disease modifying agents
- Treatment of Early PD
- Treatment of Advanced PD
- Treatment of Non-motor PD symptoms
- **Conclusions**

Conclusions

Disease-modifying research efforts
Alpha-synuclein, GBA, insulin resistance targets
Disappointing clinical results on alpha synuclein immunotherapy
Good preclinical and immunological response and CSF penetration; different routes of administration
Many Ph1-2 ongoing on different targets

Early non-motor symptoms
Old D1 receptor role
Interesting combination of DA agonists and MAOBI

Motor complications
IPX203 – new ER oral CD/LD
Role of subcutaneous pump fCD/fLD
New targets for dyskinesia: JM-010 (serotoninergic agonist)
Unilateral STN fUS: Not enough data - Unilateral PD in the context of clinical trials only
Larger stem cell trials coming

Difficult populations: Non-motor symptoms, axial symptoms, late PD > cognitive and balance trials ongoing

Exercise: Heterogeneous interventions > importance of dose, intensity and duration

Our Team


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Jonathan Jagid MD


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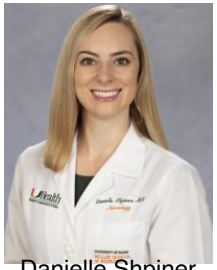

Danielle Shpiner
MD


Carlos Singer MD


Victor Riquelme
BSN MBA

Who are we?

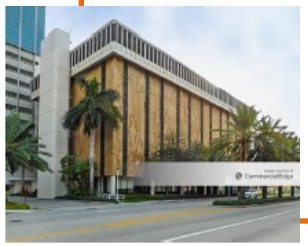
- Our vision: to provide the best care possible for patients with Parkinson's disease
- To produce excellence through teamwork
  - In the clinical sphere
  - In the research sphere

Who are our patients?

- 3700 people with Parkinson's disease
  - 2200 at Desai Sethi
  - 1500 at our other locations
- 1900 people with a Parkinsonism
  - 1700 at Desai Sethi
  - 200 at our other locations

Where we are

Sylvester at Plantation

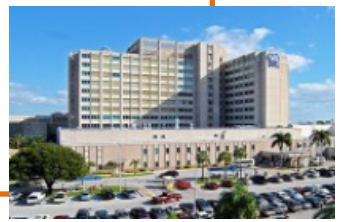


Desai Sethi Medical Center

The Lennar Foundation Medical Center

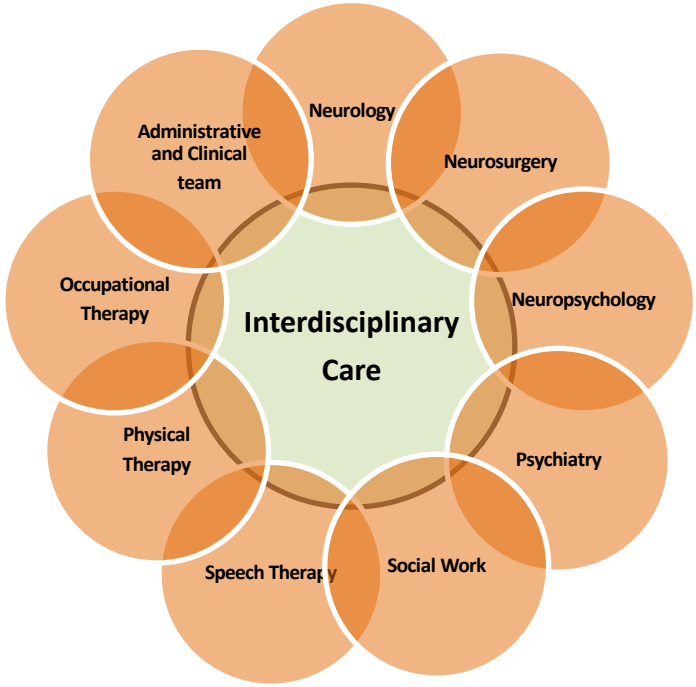
UHealth at Boca Raton

UHealth at Fort Lauderdale

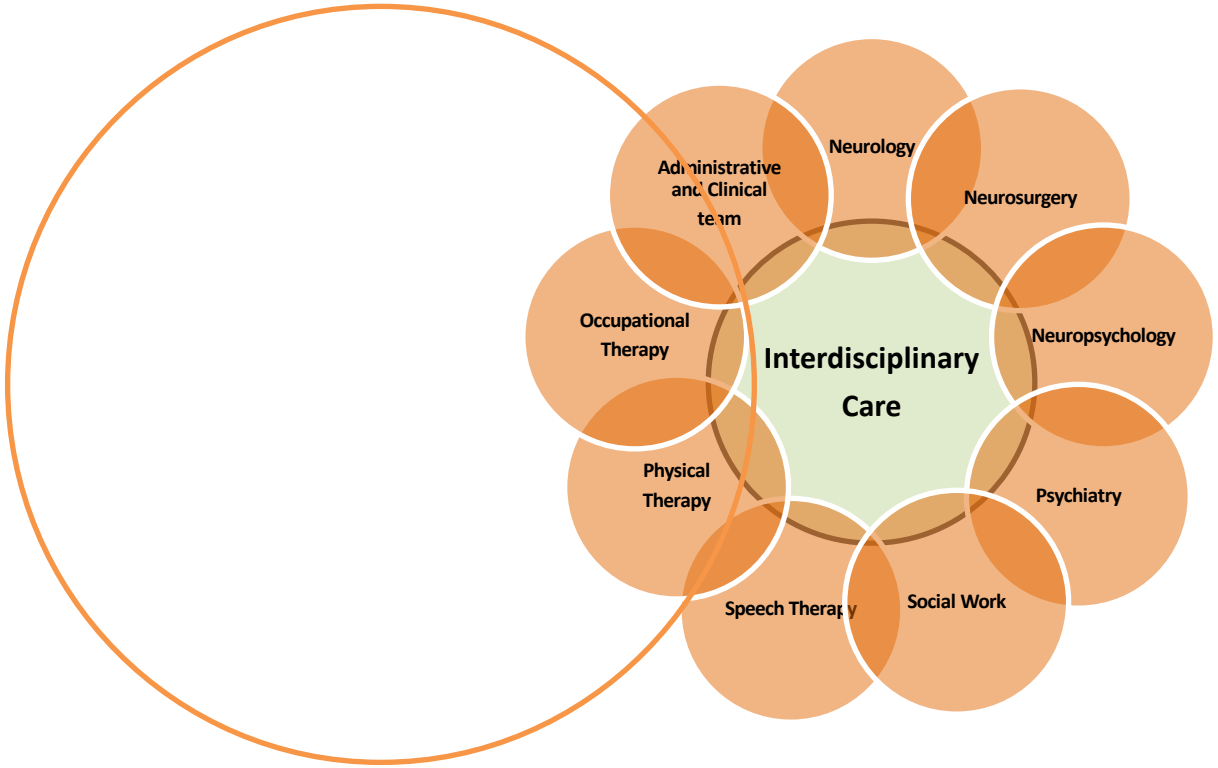


Bruce Carter VA Medical Center

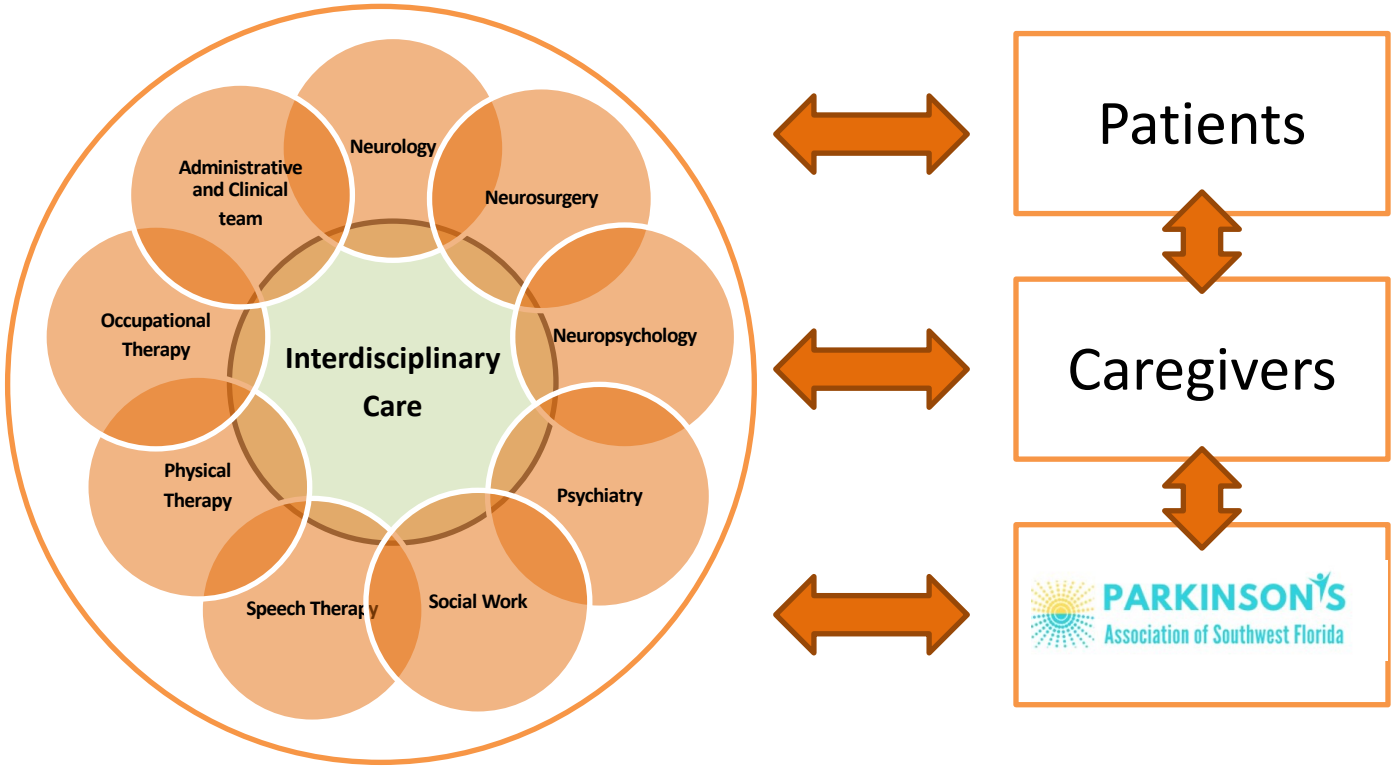
Clinical team



Clinical team



Clinical team



THANK YOU!